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7590	03/25/2010		EXAMINER	
ARNOLD & PORTER LLP			JUEDES, AMY E	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/563,956	KREMER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 29 April 2009.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 53 and 73-100 is/are pending in the application.  
 4a) Of the above claim(s) 75-77,82-87 and 100 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 54,73,74,78-81 and 88-99 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>4/22/09</u> .	5) <input type="checkbox"/> Notice of Informal Patent Application
	6) <input type="checkbox"/> Other: _____ .

## **DETAILED ACTION**

1. Applicant's amendment and remarks, filed 4/29/09, are acknowledged.  
Claims 54, 78-79, 93, 95-96, and 98-99 have been amended.  
Claim 100 has been added.  
Claims 54 and 73-100 are pending.
2. Claims 75-77 and 82-87 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species. New claim 100 is withdrawn as being drawn to a non-elected invention (i.e. a self tolerance inducing cell of group II, as set forth in the restriction requirement issued 3/17/08).  
Claims 54, 73-74, 78-81, and 88-99 are being acted upon.
3. Acknowledgment is made of applicant's amendment to the specification to clarify the claim for priority. The instant specification now indicates that the instant application is CIP of U.S. Application 10/520,931. However, the specification also indicates that the instant application is the national stage entry of PCT/EP2004/00109. As set forth in the petition decision mailed 3/12/09, the instant application has been re-processed as an application filed under 35 U.S.C. 111(a). Correction is required.
4. The rejection of the claims under 35 U.S.C. 112 first paragraph for new matter, as set forth in sections B) and C) of the previous office action, is withdrawn in view of Applicant's amendment to the claims.
5. The rejection of the claims for obviousness type double patenting is withdrawn in view of the abandonment of co-pending application 10/520,931.
6. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 93-95 stand rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method of preventing, treating, or preventing and treating a disease associated with disturbed self-tolerance comprising administering a composition comprising a tolerance inducing CD3/CD14 expressing cell, wherein said composition further comprises "a regulatory T lymphocyte that expresses a CD4 antigen and a CD25 antigen", wherein said composition comprises a multitude of tolerance inducing cells "equal in number to a multitude of said regulatory T lymphocytes", and wherein said multitude of said regulatory T lymphocytes are in a quantity of "at least  $1 \times 10^5$  cells/ml" (Claims 93-95).

Applicant indicates that support for the new claims can be found on pages 13-14, 17-19, 22-24, 26, and 29-32 of the specification.

A review of the specification fails to reveal support for the new limitations.

Regarding A), the specification on page 20 discloses that the tolerance inducing cell of the invention can be part a cell population comprising lymphocytes. This provides support for a method of administering a tolerance inducing cell composition comprising lymphocytes, but not for the method of claim 93 which recites that the cell preparation comprises "regulatory T lymphocytes expressing CD4 antigen and a CD25 antigen". The specification on pages 31-32 further discloses the tolerance inducing cells of the invention can be used in vitro to expand regulatory T lymphocytes by co-culturing equal numbers of transplant inducing cells and lymphocytes (including a quantity of at least  $1 \times 10^5$  cell/ml of said lymphocytes). The specification discloses that the co-culture results in the expansion of CD4+CD25+ T lymphocytes, and that said lymphocytes can be administered to a subject. However, the disclosure by the specification of culturing tolerance inducing cells in vitro with lymphocytes to expand CD4+CD25+ regulatory T cells for administration to a subject has a narrower scope than the instant claims. For example, the claims might encompass administering CD4+CD25+ regulatory T cells purified directly from a subject along with a tolerance inducing cell. In contrast, the specification only discloses co-culturing a tolerance inducing cell with a lymphocyte to generate said administered regulatory T cells. Additionally, the specification does not disclose administering a cell preparation comprising an equal number of regulatory T cells and tolerance inducing cells, or administering  $1 \times 10^5$  regulatory T cells per ml, as recited in claims 94-95. Rather the specification discloses culturing tolerance inducing cells with an equal number of lymphocytes in vitro (including  $1 \times 10^5$  lymphocytes/ml).

Applicant's arguments filed 4/29/09 have been fully considered, but they are not persuasive.

Applicant argues that the specification on page 19 discloses incubating lymphocytes with immune suppressive cells, and further discloses in example 7 that animals were injected with lymphocytes that had been previously co-cultivated with transplant acceptance inducing cells. Thus, Applicant concludes that the specification clearly discloses a method of administering a tolerance inducing cell composition comprising lymphocytes expressing CD4 and CD25.

As noted by Applicant, the specification discloses co-culturing *lymphocytes* with tolerance acceptance inducing cells to produce CD4+CD25+ regulatory T lymphocytes, and administering said regulatory lymphocytes. However, claim 93, as amended, recites that regulatory T lymphocytes expressing CD4 and CD25 are co-cultivated with tolerance inducing cells. This encompasses purifying a CD4+CD25+ regulatory T cell and co-culturing said regulatory T cell with a tolerance inducing cell, which is not disclosed by the instant specification. The specification only discloses co-culturing lymphocytes with a tolerance inducing cell. Lymphocytes comprise a variety of cells including CD4 T cells, CD8 T cells, and B cells. Thus "lymphocytes" have a different composition than CD4+CD25 regulatory T lymphocytes. Furthermore, as noted above, the instant specification only discloses specific cell concentrations for the co-culture and not for the administration of lymphocytes. Furthermore, said cell concentrations pertain to the concentration of lymphocytes and not of regulatory T lymphocytes, as recited in claims 94-95. For example, the specification provides support for co-culturing  $1 \times 10^5$  lymphocytes and self tolerance inducing cells for administration to the subject. The specification discloses that said-co culture will result in the production of CD4+CD25+ regulatory T cells from said lymphocytes. However, as shown in the table on page 50 of the instant specification, the lymphocyte population used for co-culture only comprises 2.65% CD4+CD25+ regulatory T cells, and after co-culture with self tolerance inducing cells, the population comprises 8.7% CD4+CD25+ regulatory T cells. Thus, co-culture with  $1 \times 10^5$  lymphocytes for administration, as disclosed by the instant specification, is not the same as co-culture with  $1 \times 10^5$  CD4+CD25 regulatory T lymphocytes, since said regulatory lymphocytes make up a very small portion of the lymphocyte population used for the co-culture.

8. Claim 81 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, It is apparent that "GM-7" hybridoma cell line of DSM Accession No. ACC2542 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines. See 37 CFR 1.801-1.809. In addition to the conditions under the Budapest Treaty, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Applicant's arguments filed 4/29/09 have been fully considered, but they are not persuasive.

Applicant argues that the amendment to the specification overcomes the rejection.

However, no assurance regarding the restrictions as to the availability of the deposit have been provided, as indicated above.

Applicant further argues that the GM-7 hybridoma is not required to practice the claimed invention.

Claim 81 is directed to a method comprising administering a specific species of self-tolerance inducing cells that express an antigen that binds to the antibody produced by the GM-7 hybridoma. Thus, the antibody is required to ensure that the administered cell comprises said antigen (i.e. either by testing for expression or by selecting said cells, as disclosed in the instant specification).

9. Claims 54, 73-74, 78-81, and 88-99 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of treating autoimmune disease comprising administering a cell that has a CD3 antigen and a CD14 antigen on the cell surface, wherein the cell is obtained

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by a process comprising isolating a blood cell population comprising monocytes, lymphocytes, and granulocytes multiplying said cell population with M-CSF, followed by cultivating said cell population with gamma-IFN, and a method for treating autoimmune disease comprising administering a cell obtained by a process comprising isolating a blood cell population comprising monocytes, lymphocytes, and granulocytes, multiplying said cell population with M-CSF, followed by cultivating said cell population with gamma-IFN,

does not reasonably provide enablement for:

a method of preventing, treating, or preventing and treating a disease associated with disturbed self tolerance comprising administering a tolerance induce cell that has a CD3 antigen and a CD14 antigen.

As set forth previously, The instant claims are drawn to a method of preventing or treating a disease associated with disturbed self-tolerance comprising administering a self-tolerance inducing cell expressing CD3/CD14 and/or made by culture in M-CSF and -IFN. The specification does not define diseases associated with disturbed self-tolerance, but discloses that said diseases include allergy and autoimmune disease. Since allergy is an aberrant immune response to a foreign antigen (and not a self antigen), it must be assumed that the diseases encompassed by the claims might reasonably encompass any type of disease involving a "disturbed" immune response. For example, the claims might encompass treating viral infections such as HIV that result in immune suppression. The claims might also encompass treating cancer, which can be result from a failure of the immune system to recognize cancerous self tissues (i.e. a disease of "disturbed" self tolerance). Thus, the claims encompass treating a wide range of diseases of different etiologies and pathological mechanisms. For example, the goal of treating cancer or viral infection is to boost the immune response, while treating autoimmune disease involves suppression of an immune response. It is unlikely that a single treatment would be effective for the broad range of diseases encompassed by the instant claims. Additionally, the instant claims encompass not only treatment, but prevention of disease. Given its broadest reasonable interpretation, "prevention" encompasses treating a subject such that no signs or symptoms of disease ever develop. However, the "prevention" of diseases such as autoimmune disease is highly unpredictable. For example, even diagnosing autoimmune disease is very difficult, and while some treatments are available a "cure" that prevents autoimmune disease has yet to be discovered (see Progress in Autoimmune Disease Research, 2005, page 7 in particular). Thus, given the difficulty in even diagnosing autoimmune disease, it would be highly unpredictable as to whether a therapy could be given to a healthy individual in order to prevent any signs or symptoms of disease from ever occurring, as is encompassed by the instant claims.

It is known that antigen presenting cells can acquire CD3/TCR complexes via transfer from T cells during co-culture (see Busch et al., 2008). The transfer of CD3 from T cells results in the detection of CD3+ APCs by FACS analysis. In fact, the instant specification demonstrates in Example 4 that the expression of CD3 by the monocytic transplantation acceptance inducing cells requires the presence of lymphocytes (i.e. T cells) during the cytokine culture. Thus, given the ability of APCs to acquire CD3 from T cells during co-culture, it is likely that the acquisition of

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CD3 depends on the presence of lymphocytes in the co-culture, but not on the particular cytokine combination used to stimulate the cells. Thus, CD3+CD14+ cells might be generated using other cytokine combinations by co-culture with lymphocytes.

Additionally, the generation of monocytes capable of suppressing an immune response is unpredictable and highly dependent on the cell culture conditions employed. For example, culture with certain cytokines results in the ability of macrophages or monocytes to support antigen-specific T cell responses, while other cytokines induce macrophages/monocytes that suppress T cells (see Mahnke et al., 2007, page 8). Furthermore, the phenotype and function of macrophages/monocytes is also affected by interaction with other cell types, including T cells (See Mahnke et al., 2007, page 8). In fact, even the effect of -IFN in combination with M-CSF (as recited in the instant claims) on monocytic cells is highly unpredictable depending on the timing of cytokine culture. For example, monocytic cells cultured with M-CSF can suppress T cells in vitro, but that effect is abrogated if -IFN is added simultaneously with the M-CSF during the culture (see Munn et al., 1996, of record, page 530 in particular). However, -IFN does not abrogate the suppressive effect of the monocytic cells if it is added after the M-CSF cultures have already been established (see page 530 in particular). Thus, the generation of cells capable of inducing tolerance is unpredictable, and is highly dependent on the particular culture conditions used. Furthermore, given the fact that monocytic cells might acquire CD3 from T-cells during co-culture, it is highly unpredictable whether any CD3+CD14+ cells (i.e. even those made by methods not involving culture with M-CSF and -IFN) would function to induce tolerance.

Thus, given the unpredictability of the art and breadth of the claims, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. The instant specification demonstrates that peripheral blood mononuclear cells comprising monocytes and lymphocytes cultured with M-CSF, followed by -IFN, are able to reduce the severity of an animal model of autoimmune colitis. The instant specification further demonstrates that a proportion of the MCS/ -IFN cultured cells are CD3+CD14+ as determined by FACS analysis. The specification does not demonstrate that these cells are responsible for suppressing colitis in vivo, nor does the specification provide evidence that any CD3+CD14+ cell (for example, those derived by transfer of CD3 onto monocytes in a co-culture with T cells in the absence of M-CSF/ -IFN) are capable of treating autoimmune disease. Furthermore, an example of treating a single autoimmune disease is not commensurate in scope with the instant claims, which encompass prevention or treatment of any disease associated with disturbed self-tolerance. Furthermore, given the state of the art in which the expression of endogenous CD3 by non-T cells is highly unpredictable. Thus, the teachings of the specification are not commensurate in scope with the instant claims, which encompass preventing or treating any disease associated with disturbed self-tolerance with any CD14 and CD3 expressing cell.

Applicant's arguments filed 4/29/09 have been fully considered, but they are not persuasive.

Applicant argues that as evidenced by Brem-Exner et al., the instant self tolerance inducing cells are effective in treating disease associated with disturbed self tolerance mediated by T cells, such as DSS-induced colitis. Thus, Applicant concludes that the claimed invention is effective against a range of disease.

The instant specification already demonstrates the effectiveness of the instant cells in treating colitis. While this may indicate the suitability of the instant cells for treatment of autoimmune disease, the instant claims broadly encompass treating any disease associated with disturbed self tolerance. As noted above, this might reasonably encompass treating cancer or viral infection. This is not commensurate in scope with the guidance provided by the instant specification, which demonstrates the suitability of the instant cells for treating an autoimmune disease.

Applicant further argues that as evidenced by Brem-Exner et al., treatment with a single dose of self tolerance inducing cells results in a statistically significant lower rate of colitis.

Brem-Exner et al. demonstrate that self tolerance inducing cells alleviate the severity of established colitis, which is not the same as "preventing" disease. As noted above, "prevention" encompasses a complete prevention such that no signs or symptoms of disease develop. In Brem-Exner et al., the treated subjects all demonstrate some degree of inflammation in the colon (i.e. a score of 1 or higher), and disease has not been "prevented".

It is noted that Applicant's amendment to the claims to limit the method of producing the cells to cultivating monocytes, lymphocytes, and granulocytes in M-CSF followed by gamma-interferon, as recited in claims 79 and 99, is sufficient to overcome a part of the previous rejection. However, said claims stand rejection for the recitation of "preventing" or treating any disease "associated with disturbed self tolerance", as discussed above. Additionally, claim 54 still encompasses treatment with any CD3+CD14+ cells. As noted above, CD3 is acquired during co-culture with T cells, and the ability of any CD3+CD14+ cell to treat disease is unpredictable and highly dependent on the culture conditions used to produce the cell. For example, culture of lymphocytes and monocytes with IFN-gamma alone would likely result in the acquisition of CD3 by said monocytes (i.e. the production of a cell that has a CD3 and CD14 antigen on the cell surface). However, given the state of the art, as noted above, said cell would not be expected to treat autoimmune disease. Thus, it would require undue

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experimentation to treat disease associated with self tolerance using any cell that has CD3 and CD14 on the surface, as broadly encompassed by the instant claims.

10. The following are new grounds of rejection necessitated by Applicant's amendment.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 78-79 and 99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 78-79 and 99 recite the limitation wherein said lymphocytes and granulocytes in step (a) comprise from about 10% to 50% of "the total population of cells" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. Additionally, step (a) recites obtaining a monocyte, a lymphocyte, and a granulocyte, which appears to indicate that a single cell of each type is cultured. It is unclear how a single lymphocyte and a single granulocyte can comprise 10-50% of a cell population comprising only 3 cells. It is suggested to amend step (a) of claims 78-79 and 99 to recite obtaining a population of cells comprising monocytes, lymphocytes, and granulocytes from the blood.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amy E. Juedes

Patent Examiner

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Primary Examiner, Art Unit 1644